Final Technical Report

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Center Name: University of Rochester–EPA PM Center
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Title: Inflammatory Responses and Cardiovascular Risk Factors in Susceptible Populations
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RFA: Airborne Particulate Matter (PM) Centers (1999)
Research Category: Particulate Matter

Objective(s) of the Research Project: The aim of the Rochester Particle Center epidemiological studies was to assess the short-term health effects of fine and ultrafine particles on vascular and cardiac function. It was hypothesized that patients with coronary artery disease (CAD) as well as chronic obstructive pulmonary disease (COPD) would be susceptible to ambient fine and ultrafine particles. The hypothesis at the time was that the underlying systemic inflammation due to atherosclerotic disease would render CAD subjects more vulnerable. In contrast, subjects with COPD would be more vulnerable due to chronic inflammatory pulmonary disease. As the size and the composition of the particles are determined by the sources of the particles it is important for regulatory purposes to better understand the relative importance of sources in association with health effects. We had the following specific aims:

1) Blood markers of exacerbation of chronic inflammation and altered vascular function are elevated in association with ambient particles.

2) Cardiac function in patients is altered in association with ambient air pollution.

3) Particles from traffic and other combustion sources are associated with vascular and cardiac effects.

Summary of Findings: Two epidemiological studies were conducted to assess short-term health effects of fine and ultrafine particles in 61 patients with coronary artery disease and in 39 patients with COPD in Erfurt, Germany as part of the Rochester Particle Center. Twelve clinical visits including ECG measurements and blood withdrawals were scheduled. Ninety-eight percent of all scheduled ECG recordings and 94% of all scheduled blood withdrawals were realized.

Statistical Analyses

Continuous outcomes such as measurements of the blood coagulability, heart rate variability (HRV), and lung function measures were analyzed based on linear regression models considering repeated measurements for the subjects. The distribution of the residuals was checked carefully and additional analyses converting the continuous measurements into binary variables were conducted in case the residuals were not approximately normally distributed. These variables were analyzed using logistic regression analyses. In particular, several approaches to model the dose-response functions were applied including parametric, semi-parametric and non-parametric methods. The lag structure of the association between the air pollutants and the outcomes was analyzed to evaluate the time lags between exposure and response. Based on the experimental and clinical data collected in the other Cores, specific hypotheses were formulated before the analyses and then tested in the epidemiological data (*specific aims 1 and 2*). The results obtained for the different sources will be compared to the results of the contributing particle fractions or gaseous pollutants (*specific aim 3*). It is unlikely that there is sufficient power to test for differences between regression coefficients for single pollutants and for specific sources. However, the biomarkers of cardiac function exhibit different response profiles when $PM_{2.5}$, ultrafine particles and organic or elemental carbon are considered. Additional information on source contributions will help to elucidate the role of different particle properties responsible for cardiovascular disease exacerbation via different mechanisms.

Specific Aim 1-Blood Biomarker. There was also evidence for an increase in C-reactive protein (CRP) concentrations and a shift to a more pro-coagulating state of the blood (Ruckerl, et al., 2006). For the CAD panel, an additional marker of inflammation was determined by the Immunology Core. Soluble CD40 ligand had been selected as a marker for exacerbation of chronic inflammation and altered vascular function (Phipps, 2000).

Our findings suggest an increase in sCD40L in association with ambient air particles, particularly with elevated levels of ultrafine particles and accumulation mode particles. For platelets the effects were limited to ultrafine particles showing an immediate as well as a three days delayed decrease. The regression of leukocytes showed consistently negative associations for UFP, AP, and $PM_{2.5}$, with lag 0 and for AP in addition with lag 3 and the 5-day average. As the effects seemed to be limited to the 24 hours prior to the blood withdrawal, we split the 24 hours up into four 6-hour periods and analyzed the results for UFP. While the effect for sCD40L was most prominent for the time period 12 to 17 hours prior to the blood withdrawal, platelets and leukocytes showed an immediate decrease in the first 5 hours and a delayed one between 18 to 24 hours (Figure 1) (Ruckerl, et al., 2007).

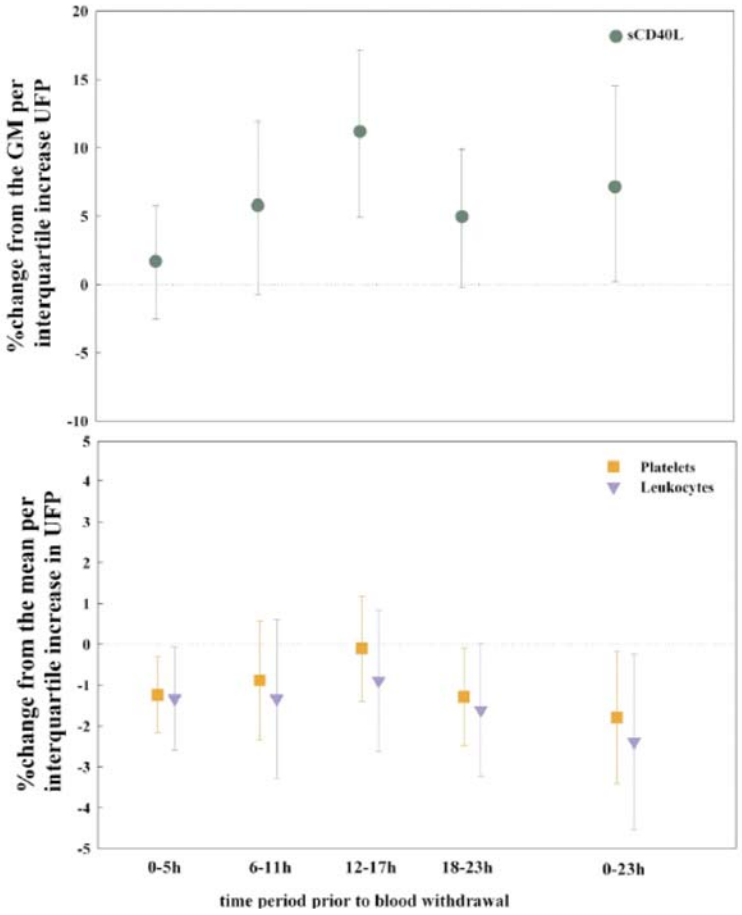

Figure 1. Effects of UFP and PM on Blood Biomarkers and Blood Cells in CAD Patients (Ruckerl, et al., 2007).

Erythrocytes and hemoglobin in contrast seemed to react more to the larger particles size fractions $PM_{2.5}$ and PM_{10}, showing a decrease in association with higher levels of air pollution. The largest negative effects for the erythrocytes were seen for PM_{10} for lag 2 and the 5-day-average exposure, a finding that is reflected to a lesser extent in the results of the hemoglobin.

For the COPD panel, differential hemograms were available. Preliminary results suggest no effect of particulate matter on all leukocytes combined. However, an increase in neutrophilic bandform granulocytes was observed in association with PM_{10} and AP immediately as well as with a 5-day average. Other leukocytic cell rows were either unaffected or showed small decreases. These results may provide evidence for a stimulation of the bone marrow by particulate matter (Socher, et al., 2005).

Specific Aim 1-Interdependence of Blood Markers and Cardiac Function. Additionally, associations within ECG recordings (time- and frequency-domain of HRV and repolarization parameters) and associations within blood markers (acute phase response, endothelial cell activation, and coagulation state markers) as well as associations between ECG recordings and

blood markers were analyzed using generalized estimating equation models adjusting for repeated measurements. Within the ECG recordings, strong significant associations were found between time- and frequency-domain parameters, and moderate but also significant associations between frequency-domain and repolarization parameters. Within blood markers, strong but significant associations existed between CRP and fibrinogen, D-dimer, E-selectin, ICAM-1, and SAA.

Between ECG recordings and blood markers, repolarization parameters and acute phase response proteins showed moderate but significant associations. HRV parameters and endothelial cell activation markers were significantly but only weakly associated. The results indicate the interplay between the autonomic nervous system and myocardial substrate as well as interactions of the acute phase response with endothelial cell activation and coagulation state. While ECG parameters and blood markers seem to vary independently, there was the suggestion for a link between systemic inflammation and repolarization as well as endothelial dysfunction and HRV (Yue, et al., 2006).

Specific Aim 2-HRV. In a study in patients with CAD, the autonomic control of the heart was altered in association with $PM_{2.5}$ and organic (OC) and elementary carbon (EC) concentrations of $PM_{2.5}$ (Ibald-Mulli, 2005). These findings highlight the importance of the carbonaceous component in particles. Furthermore, we were able to detect changes in the repolarization of the heart in association with $PM_{2.5}$ and the number concentrations of accumulation mode particles (AP) (Henneberger, et al., 2005). Regarding arrhythmia, the number of supraventricular and ventricular runs showed strong effects correlated to AP and ultrafine particles as well (Berger, et al., 2006). Thereby, we found the first evidence that particles also might increase cardiac vulnerability and might modify the cardiac substrate. The effects of particulate air pollution on the autonomic nervous system as measured by heart rate (HR) and HRV in patients suffering from COPD were analyzed. Low frequency (LF) and the ratio of low to high frequency (LF/HF) increased in association with an increase in PM_{10}, OC, and EC during the 24 hours before the ECG measurement (Figure 2). Consistently, there was a significant decrease in heart rate with an increase of all particles measured 0-23 hours before the ECG recording. The analysis also showed a significant increase in root mean square successive difference (RMSSD) in response to an increase in all particle concentrations and some gases during 48-71 hours before the ECG recording. These results are contradictory to prior findings in CAD patients and our initial hypothesis. Taking both findings into account it is conceivable that the air pollution reaction depends on the disease status of the patient and that elevated concentrations of ambient particles are associated with a disturbance of the autonomic heart control manifested by an increased HRV in patients with COPD (Bero Bedada, et al., 2005).

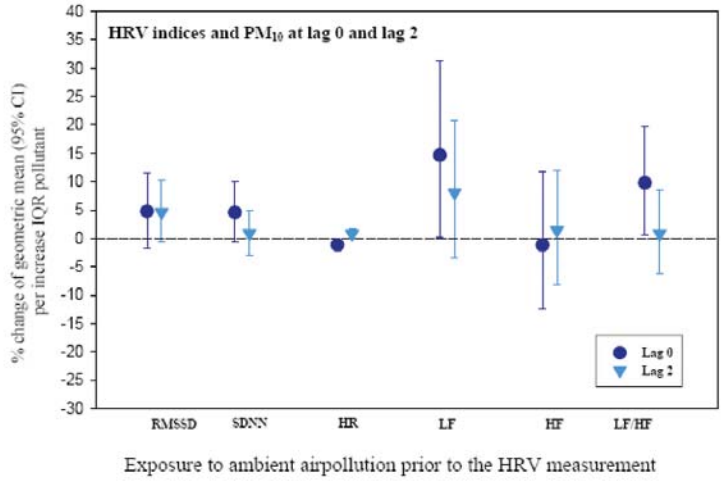

Figure 2. Effects of PM_{10} on Heart Rate and Heart Rate Variability Parameters

Specific Aim 4-Effects of Traffic on Myocardial Infarction. A complete series of myocardial infarction survivors registered between 1999 and mid 2001 was interviewed to collect information on activities during the 4 days before MI onset. Analyses considered ambient particle concentrations as well as diary data. A total of 691 subjects were interviewed and they showed a higher prevalence of time spent in traffic 1 hour before the onset of myocardial infarctions than 24 to 72 hours earlier (Figure 3). Time spent in traffic was associated with MI onset 1 hour later (OR=2.9 (95% CI: 2.2 to 3.8) (Peters, et al., 2004). These associations were seen for times spent in cars (OR=2.6 (95% CI: 1.9 to 3.6), times spent in public transport (OR=3.1 (95% CI: 1.4 to 6.8) and on bicycles (OR=3.9 (95% CI: 2.1 to 7.2). Ambient $PM_{2.5}$ concentrations at the urban background site also suggested an association with MI onset 2 days later (RR: 1.09 for 10 $\mu g/m^3$ $PM_{2.5}$ (95% CI: 0.98 to 1.20) (Peters, et al., 2005).

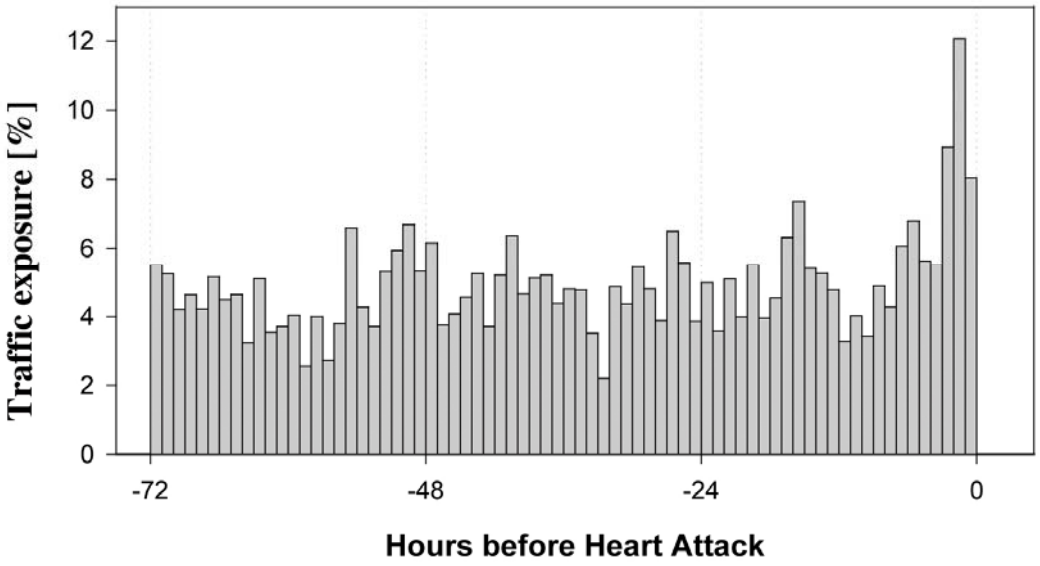

Figure 3. Prevalence of Time Spent in Traffic in 691 MI Survivors During the 72 Hours Before MI Onset

Specific Aim 3-Source Apportionment. Sources of fine and ultrafine particles were analyzed to determine the size distribution of fine and ultrafine particles. All analyses were conducted in collaboration with Core 1. The aim of this study was to use fine particle size distribution data collected between September 1997 and August 2001 in Erfurt, Germany, to investigate the sources of ambient particulate matter by positive matrix factorization (PMF). A total of 29,313 hourly averaged particle size distribution measurements covering the size range of 0.01 to 3.0 µm were included in the analysis. The particles number concentrations ($1/cm^3$) for the 9 channels in the ultrafine range, and mass concentrations (ng/m^3) for the 41 size classes of accumulation mode and fine particles were used in the PMF. The analysis was performed separately for each season. Additional analyses were performed including calculations of the correlations of factor contributions with gaseous pollutants (O_3, NO, NO_2, CO, and SO_2) and particle composition data (sulfate, organic carbon, and elemental carbon), estimating the contributions of each factor to the total number and mass concentration, identifying the directional locations of the sources using the conditional probability function, and examining the diurnal patterns of factor scores. These results were used to assist in the interpretation of the factors. Five factors representing particles from airborne soil, ultrafine particles from local traffic, secondary aerosols from local fuel combustion, particles from remote traffic, and secondary aerosols from multiple sources were identified in all seasons. The results can be used in epidemiological studies to investigate adverse health effects of source-specific particulate matter (Yue, et al., 2007a)

We used 56 patients' 5-minute ECG recordings for the analysis of repolarization parameters QT interval and T wave amplitude, and 57 patients' plasma samples to determine the biomarkers von Willebrand factor (vWF) and CRP. Linear and logistic regression models were used to analyze the associations between five particle source factors (airborne soil, local traffic ultrafine particles, combustion aerosols, diesel traffic particles, and secondary aerosols) and these health

parameters adjusting for trend, weekday, and meteorological variables. An increase in QT interval and a decrease in T wave amplitude were observed in association with traffic-related particles exposure during 0-23 hours before the ECG recordings. The inflammatory marker vWF increased in association with both traffic-related particles and combustion aerosols at different exposure lags. All source particles had positive associations with CRP levels above the 90th percentile (8.5 mg/l). These results suggest that traffic-related and combustion-generated particles show stronger adverse health impact with regard to cardiac effects, and that different source particles may have the potential to cause an acute phase response in these patients (Yue, et al., 2007b)

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Supplemental Keywords: NA

Relevant Web Sites: http://www2.envmed.rochester.edu/envmed/PMC/indexPMC.html